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ARTICLE

Inhibitory Neurophysiological Deficit as a Phenotype for Genetic Investigation of Schizophrenia

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Many investigators have proposed that biological endophenotypes might facilitate the genetic analysis of schizophrenia. A deficit in the inhibition of the P50 evoked response to repeated auditory stimuli has been characterized as a neurobiological deficit in schizophrenia. This deficit is linked to a candidate gene locus, the locus of the α7-nicotinic cholinergic receptor subunit gene on chromosome 15q14. Supportive evidence has been found by other investigators, including: 1) linkage of schizophrenia to the same locus; 2) linkage of bipolar disorder to the locus; and 3) replication of the existence of this neurobiological deficit and its relation to broader neuropsychological deficits in schizophrenia. It is certain that there are many genetic factors in schizophrenia and bipolar disorder; what is needed is a complete and precise description of the contribution of each individual factor to the pathophysiology of these illnesses. J. Med. Genet. (Semin. Med. Genet.) 97:58–64, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

A complex illness is one that does not result from a single genetic abnormality. Complexity is not only obvious from schizophrenia's non-Mendelian inheritance pattern, but it is also the likely situation for an illness that has no single defined biological deficit [Tsuang et al., 1990]. After several major efforts, the current findings consist of many linkage signals of moderate effect on several different chromosomes [Cao et al., 1997; Blouin et al., 1998]. Similarly, despite intensive studies using a variety of different techniques, no single biological abnormality has emerged as the major pathogenic factor. These two conundrums may well reflect the same problem, i.e., schizophrenia likely results from the interaction of several genetic and non-genetic pathogenic factors. A central thesis of our work has been that one solution to the dual genetic and biological complexity is to attempt to solve both of them simultaneously for discrete elements within schizophrenia itself. Linkage of a putative brain deficit in schizophrenia to a specific chromosomal site provides strong evidence that the deficit is indeed a discrete neurobiological dysfunction in the illness. Conversely, the most powerful phenotypes for linkage are likely to be discrete neurobiological deficits that result from the effect of a single gene. Although this strategy has not been widely used in schizophrenia, it has been successful in a number of other genetic illnesses, that, like schizophrenia, cluster in families but do not have Mendelian inheritance. Hemochromatosis is perhaps the best known; serum ferritin proved to be a better marker of genetic affection than the illness itself [Borecki et al., 1990]. Another example is colon cancer, where the expression of polyps, rather than clinical cancer itself, is the inherited phenotype [Leppert et al., 1990].

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THE SEARCH FOR A PHENOTYPE

Many investigators conceptualize schizophrenia as arising from more basic cognitive deficits. The biological bases of cognitive deficits in schizophrenia, however, are unknown and

One solution to the dual genetic and biological complexity is to attempt to solve both of them simultaneously.

are likely to be highly complex. Nearly every brain region, including the frontal and temporal lobes, the cerebellum, striatum, and thalamus, has been proposed to be involved. [Tamminga et al., 1992; Nelson et al., 1998; Andreasen et al., 1999;]. This panoply of biological abnormalities have made it difficult to assign specific deficits to specific causes. A possible simplification is to separate genetic from non-genetic influences. Therefore, several investigators, including ourselves, have attempted family studies, in which neuropsychological deficits have been isolated in members of the pedigree with varying degrees of genetic risk. Deficits in attentional function, for example, have been observed by us in parents of schizophrenics who have ancestral family histories of schizophrenia [Harris et al., 1996], and by others in children of schizophrenic mothers [Freedman et al., 1998], in siblings of schizophrenics [Cannon et al., 1994], and in clinically unaffected monozygotic twins of schizophrenics [Goldberg et al., 1990].

An even more elementary level of analysis is to consider biological deficits that might reflect deficits in a single neuronal mechanism. At this simpler level, there is the possibility of isolating a discrete deficit that might reflect the activity of a single gene. A number of biological deficits are shared by schizophrenics and their relatives. A variant of segregation analysis was used to show that eye movement deficits are the phenotype for a single gene effect that also conveys risk for schizophrenia [Holzman et al., 1988], and linkage of eye movement deficits to the site of a previously known linkage for schizophrenia was demonstrated [Arolt et al., 1996]. Other deficits that are found in families include increased reaction time abnormalities [de Amicis et al., 1986], neuropsychological abnormalities [Cornblatt and Keilp, 1994], abnormalities in the P300 auditory evoked potential [Sham et al., 1994], and ventricular enlargement [Shihabuddin et al., 1996]. Our work on the P50 inhibitory deficit as an alternative phenotype is described below. To date, it is the only physiological abnormality whose linkage analysis has pointed to a specific candidate mechanism for neuronal dysfunction in schizophrenia [Freedman et al., 1997].

IDENTIFICATION OF AN INHIBITORY SENSORY GATING DYSFUNCTION IN SCHIZOPHRENICS AND THEIR RELATIVES

We applied the classical neurophysiological conditioning-testing paradigm, designed to study inhibition, to auditory evoked responses in schizophrenia [Adler et al., 1982]. Our goal was to identify an elementary neuronal function that could be studied in both humans and animal models. In this paradigm, pairs of identical stimuli, termed conditioning and test, are presented to the subject at various intrapair intervals. We discovered that at a range of intervals, including 500 msec, normals diminish the amplitude of the P50 wave response to the second or test stimulus, whereas schizophrenics have similar responses to both. Consistent differences in the inhibition of the P50 response between schizophrenics and normal subjects have been reported by us [Waldo et al., 1994; Griffith et al., 1995], by others to whom we introduced the paradigm [Ward et al., 1996], and by independent groups who have used similar or identical paradigms [Boutros et al., 1991; Erwin et al., 1991; Judd et al., 1992; Jin et al., 1997; Clementz et al., 1998; Yee et al., 1998]. The inhibition is generally measured as the ratio of the amplitude of the test to the conditioning response. Figure 1 shows sample waveforms from four schizophrenic subjects and their parents. The P50 wave is identified and its amplitude measured relative to the preceding negativity by a computer algorithm [Nagamoto et al., 1989]. Families were chosen for this study to have apparent unilineal family histories of schizophrenia [Waldo et al., 1995]. In each case, the schizophrenic proband has a ratio of the amplitude of the test to the conditioning response greater than

A number of biological deficits are shared by schizophrenics and their relatives.

50%, that is generally the upper limit of normal values. This deficit in inhibition is shared by the parents who have an ancestral family history of schizophrenia, but not by the parents without such histories. A deficit in P50 inhibition correlates with neuropsychological evidence for a deficit in attention [Cullum et al., 1993; Erwin et al., 1998; Yee et al., 1998]. This feature of neuropsychological disability is also one of the familially transmitted aspects of schizophrenia [Goldberg et al., 1990; Cannon et al; 1994; Harris et al., 1996; Freedman et al., 1998].

BIOLOGICAL STUDIES POINT TO THE α7-NICOTINIC RECEPTOR

The biological basis of the inhibitory abnormality was investigated in a parallel series of basic and clinical experiments. Briefly, the basic investigations showed that hippocampal pyramidal neurons are the source of the P20-N40 wave, the rodent equivalent of human P50 [Bickford-Wimer et al., 1990;

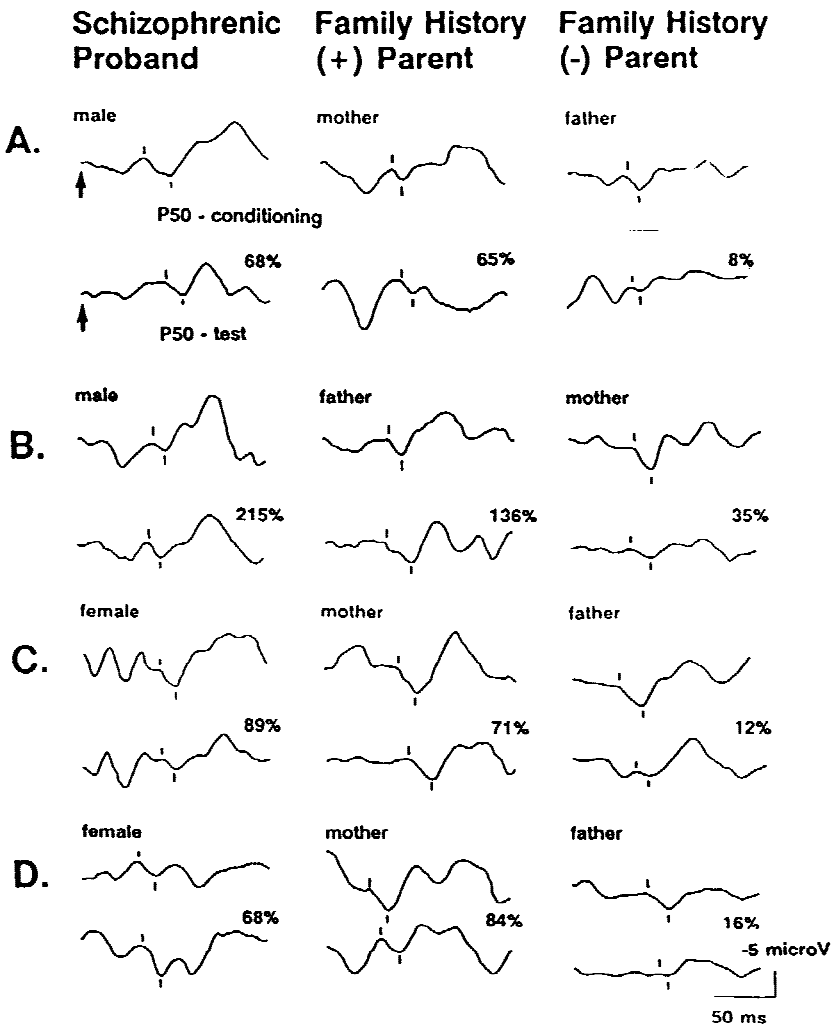

Figure 1. Evoked potential recordings from four nuclear families (**A–D**) with a schizophrenic offspring. The recordings show the conditioning and test responses. The P50 wave is indicated in each response by the computer generated tic below each wave and was measured relative to the preceding negativity indicated by the tic above. The percentage ratio of test to conditioning P50 amplitude is shown for each subject [from Waldo et al., 1995].

Miller et al., 1995]. The inhibition of response to the second stimulus is presynaptic, mediated by $GABA_B$ receptors on glutamatergic afferents [Hershmann et al., 1995]. To release sufficient GABA release to activate these receptors requires cholinergic activation of hippocampal interneurons via the reticula-septal pathway, mediated by α7-nicotinic receptors that we have shown to be localized on these interneurons [Freedman et al., 1993; Bickford et al., 1993; Miller et al., 1993, 1995; Breese et al., 1997; Frazier et al., 1998]. These receptors admit calcium to the interneurons, that produces nitric oxide, that in turn acts as a second messenger to prolong the effect of receptor activation on neuronal function [Adams and Stevens, 1998]. Loss of inhibition in animal models is produced by lesion of the cholinergic afferents, pharmacological blockade of the α7-receptor, genetic deficiency in the α7 receptor in inbred mouse strains, or blockade of nitric oxide production by the α7 receptor [Luntz-Leybman et al., 1992; Bickford et al., 1995; Stevens et al., 1996; Adams and Stevens et al., 1998].

This deficit in inhibition is shared by the parents who have an ancestral family history of schizophrenia.

Several clinical correlates of these basic science findings have been observed. First, α7 nicotinic receptor-mediated regulation of inhibition of auditory P50 response has been observed in schizophrenia. In schizophrenics and their relatives, nicotine transiently normalizes the deficit in P50 inhibition [Adler et al., 1992, 1993], as predicted from the animal model, with a pharmacology consistent with activation of the α7 receptor, i.e., failure of blockade by the muscarinic antagonists or the high affinity nicotinic receptor channel blocker mecamylamine [Freedman et al., 1994]. Furthermore, schizophrenics

can normalize not only this abnormality, but eye tracking abnormalities as well, at doses of nicotine that they achieve through their particularly heavy smoking [Olincy et al., 1997, 1998].

GENETIC LINKAGE OF PATHOPHYSIOLOGICAL DEFICITS IN SCHIZOPHRENIA ON CHROMOSOME 15

Several analyses of schizophrenics and their relatives characterized the heritability of the P50 inhibitory deficit [Waldo et al., 1994, 1995]. The finding of P50 inhibitory deficits in relatives of schizophrenics has been replicated by others [Clementz et al., 1997]. A preliminary genome-wide scan in multiplex schizophrenia families identified several areas that showed evidence for linkage of both the inhibitory deficit and schizophrenia, including chromosome 15q14 [Coon et al., 1993]. This area was subsequently discovered by another group to contain the α7 nicotinic receptor subunit gene [Chini et al., 1994]. Therefore, we isolated a new polymorphic marker (D15S1360) from a 180 kb YAC containing the α7 human gene. A second genome wide scan was performed in 9 multiplex families that yielded only one significant lod score ($P < 0.001$, verified by simulation), that exceeded 5.0 at D15S1360 without recombination for both two point and multipoint analyses. The lod score for schizophrenia was positive, but did not exceed 3.0. The difference reflects the reduced power of the schizophrenia phenotype, that was less than 50% penetrant. Thus, although a single allele of D15S1360 was generally co-inherited with both schizophrenia and the P50 inhibitory deficit, the number of persons with schizophrenia was less than the number with the P50 deficit, only some of whom were schizophrenic. Hence, the lod scores for the two traits were both positive, but of different magnitude [Freedman et al., 1997].

We have conducted additional studies in the NIMH Genetics Initiative families to determine if there is further support for the initial linkage. Although these families have not been phenotyped for the P50 abnormality, they have been rigorously and independently diagnosed for schizophrenia. We found significant D15S1360 allele sharing among affected sib pairs ($P < 0.0024$) using SIBPAL [Leonard et al., 1998]. The NIMH group itself [Kaufmann et al., 1998] independently reported significant evidence for linkage in non-parametric analyses at ATC3C11, their only marker in the region. Two groups reported failures of replication at the marker we developed for this locus: one found an NPL score of 0.3 in schizophrenia and subsequently found linkage disequilibrium with the same marker in bipolar families [Neves-Pereira et al., 1998], and the other reported a lod score of 0.75 at the flanking highly polymorphic marker ACTC [Curtis et al., 1999]. Other groups have now shown inheritance at the 15q14 locus for bipolar disorder [Edenberg et al., 1997], one of them using markers specifically designed by us to examine the α7 nicotinic receptor locus [Neves-Pereira et al., 1999]. Several genetic loci have shown overlap between findings for bipolar disorder and schizophrenia, and the possibility that the two illnesses are part of the same spectrum has been raised by many investigators [Berrettini et al., 1997]. We have previously shown overlap between the P50 inhibitory deficits in bipolar disorder and schizophrenia in three studies [Adler et al., 1989, Baker et al., 1990]. Given the new genetic findings, further examination of the similarities and differences in phenotype associated with the α7 nicotinic receptor locus is warranted.

The α7 nicotinic receptor is thought to be a homopentamer in vitro; its in vivo structure is unknown. The gene is homologous across species and contains 10 exons. Humans, however, have a partially duplicated portion, that is about 1 million bases centromeric and thus within the linkage support region. It contains 4 novel exons, followed by exons 5–10 of the α7 gene [Gault et al., 1998]. Examination of the α7 gene and its duplication to determine if there are indeed molecular alterations in the gene in schizophrenics is in progress.

BILINEAL INHERITANCE OF PHYSIOLOGICAL ABNORMALITIES IN CHILDHOOD ONSET SCHIZOPHRENIA

The inheritance of D15S1360 and the segregation of the P50 abnormality follow an apparent autosomal dominant pattern, so that most schizophrenics are expected to be heterozygous for any pathogenic allele. The data, however, do not exclude the possibility of co-dominance, a less common state in which individuals who have two pathogenic alleles have increased disability and, often, an earlier onset of illness. We hypothesized that childhood-onset schizophrenia might be the manifestation of co-dominance at the chromosome 15 locus. The severity of this illness initially resulted in it being considered a pan-developmental abnormality, perhaps unrelated to adult onset illness. More recently, phenotypic similarities between adult and childhood-onset illnesses have been emphasized [McKenna et al., 1994]. In many genetic illnesses, patients with increased severity and earlier onset have increased genetic risk, and that possibility has been raised for childhood onset schizophrenia [Rutter et al., 1999].

We have phenotyped 10 nuclear families with both the P50 paradigm and smooth pursuit eye movements. In contrast to families of adult onset probands, who almost always show unilineal presence of the P50 inhibitory deficit in the parents of the probands, i.e., only one parent affected [Waldo et al., 1994, Ross et al., 1998], the families of the childhood onset probands generally show bilineal presence of the P50 inhibitory deficit, i.e., both parents affected [$P < 0.006$; Ross et al., 1999]. A similar pattern is observed with one of the smooth pursuit eye movement deficits, an increase in the level of small leading saccades. In addition, the severity of the eye tracking deficit in the childhood onset-probands

was twice as great as that found in adult onset probands or in the children's parents. These findings thus support the hypothesis of possible co-dominant inheritance in childhood onset schizophrenia.

GENOCOPIES OF THE LINKAGE AT THE α7 NICOTINIC RECEPTOR LOCUS

Genocopies for schizophrenia are not common, but there have been reports of schizophrenic like illnesses near the chromosome 15q14 α7 nicotinic receptor locus, associated with a variety of genetic abnormalities. For example, a recent cytogenetic investigation implicates the chromosome 15q14 region in two cases of schizophrenia in an extended pedigree [Calzolari et al., 1996]. In this family, meioses involving a balanced translocation with a breakpoint at 15q13–14 produced a satellite chromosome in two cousins whose mothers both carried the translocation. Both individuals developed schizophrenia, that

These findings thus support the hypothesis of possible co-dominant inheritance in childhood onset schizophrenia.

was otherwise not present in the family's history. Three other genetic illnesses linked to this chromosomal region have been reported to co-express psychoses resembling schizophrenia in some individuals: Prader–Willi syndrome, a disease involving deletion or abnormal imprinting of genes at 15q11–12, Marfan syndrome that generally involves mutation of the fibrillin gene at 15q21, and Andersmann agenesis of the corpus callosum, that is caused by a deletion at chromosome 15q15 [Sirota et al., 1990; Clarke, 1993; Casaubon et al., 1996]. Either cosegregation of nearby genetic defects on chromosome 15 or a common defect that affects expression of several genes in this region could be responsible for co-expression of schizophrenia with these illnesses.

SUMMARY

Initial neurobiological and genetic evidence of inheritance of a physiological abnormality related to schizophrenia has been obtained, that implicates the α7 nicotinic receptor gene. Bilineal inheritance may be associated with more severe, earlier onset illness. Replication of these findings, identification of the molecular abnormality in the gene, and determination of the full role of the abnormality in psychotic illnesses are necessary next steps to determine the role of this gene in the pathogenesis of schizophrenia.

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